Attachment III

Attachment III – Preclinical and Clinical Findings

In an effort to address the Agency's point to consider regarding presentation of literature articles that may be unfavorable to the petition, literature existing in the original petition's search was reevaluated (Attachment I) and a new search was conducted (Attachment II). The findings are discussed in this attachment. The preclinical work included investigations into the effects of various output parameters in animals and *in vitro* systems. The results, as one would expect, varied among the test systems and output parameters used, suggesting that *in vitro* models must be carefully selected, and that a combination of animal and *in vitro* work should be conducted when exploring a new signal. The additional clinical evidence described below supports reclassification (one article with a small study population was inconclusive regarding the performance of an unidentified device).

Preclinical Findings

Much of the preclinical work identified in the search describes research in animal models and *in vitro* systems to investigate the safety and effectiveness of various output parameters. There are also studies in cell culture systems designed to examine the mechanism(s) of action of various electrical stimuli in bone repair processes and the types of cells that may be recruited or respond to the stimulus. This type of preclinical testing is included in the preclinical analysis and testing section of the proposed guidance document. Bear in mind that unsuccessful studies in animal and organ or cell culture system models are not unfavorable to the petition, but simply show the desire for expanding the knowledge base related to the mechanisms involved and the potential effectiveness of proposed output parameters (Aaron, Ciombor and Simon 2004, Attachment III). Scientists know that stimulation can be effective, but the mechanisms by which this is accomplished continue to be studied.

The articles demonstrate that effectiveness may vary among test systems and varying output parameters used. Examples of published reports are provided in the tables below. These types of reports were obtained in the initial search conducted by the petitioner, however, the petition focused mainly upon publicly available <u>clinical</u> reports and experience related to device safety and effectiveness, rather than the details presented in preclinical studies. Expanded searches also revealed these reports. Exclusion of these articles from the original petition was not based upon deliberately ignoring the existence of such information, but rather due to the focus on clinical information.

<u>Cellular Level</u>

Articles related to past and continued study of the interactions of the electric and electromagnetic fields at the cellular level were in the original search (Torricelli et al., 2002; Goodman et al., 1983; and Hinsenkamp et al., 1978; and, Guerkov et al., 2001) as well as the expanded searches (Brighton et al., 1992; Lohman et al., 2000; Fitzsimmons et al., 1992; Bodamyali et al., 1998; Yamamoto et al., 2003; Hartig et al., 2000; Spadaro and Bergstrom, 2002; Diniz et al., 2002; and, Aaron et al., 2004). These citations are intended as examples and not as a comprehensive list of literature representing this field.

Such reports represent efforts to determine: the sequence of events which occurs as a result of electrical stimulation; the interaction of the fields at the level of the cell membrane with regard to ion channels and receptor interaction; signal transduction; and, cell types that respond and those that do not. The regulation and concentrations of calcium at the cellular level are also studied. Subsequent effects on DNA and RNA synthesis in gene expression for and of growth factors (i.e., BMPs, TGF_{β} 1, IGF-II, prostaglandins) also appear to be involved. These actions can increase proliferation and/or differentiation, depending upon cell type, and ultimately result in increased matrix synthesis. Negative results reported for certain cell lines or cell types do not constitute unfavorable data with respect to the overall device effects. Interpretation of these data as they relate to the larger picture is required. Perhaps the particular cell type examined is not involved or recruited in the process. Growth factor production may also vary at different times in the process depending upon the point at which a cell type is involved in the process and what is involved in the matrix production. This body of work does not represent evidence which may be unfavorable to the petition. In fact, it represents a continuing effort in the study of cell biology and the effects of internal and external electrical and electromagnetic effects.

Table 1. Examples of Preclinical Articles Related to Mechanism of Action Studies

Reference	Cell Type	Electric Field	Results
Fini et al., 2005	Articular cartilage (chrondocytes)	PEMFs	Increase proliferation and matrix synthesis
Aaron et al., 2004		Capacitive coupling Inductive coupling	Increase proliferation, Increase TGFb mRNA, BMP-2,-4 mRNA Increase proliferation: Increase TGFb mRNA and protein,
Torricelli et al., 2003	MG63 human osteoblast-like cells + poly-methylmethacrylate (PMMA) + PMMA alpha tricalcium phosphate	PEMF – 75 Hz, 2.3mT, 1.3ms pulse duration 12 h/day for 3 days	Assess biological response at cell-biomaterial interface Improved proliferation Activation (ALP, OC Differentiation
Yamamoto et al., 2003	Rat calvaria osteoblasts UMR 106 cells ROS 117/2.8 cells	Static magnetic field 160mT	Stimulates differentiation and activation Increase area and Number of mineralized nodules No increase in cell proliferation

Table 1. Examples of Preclinical Articles Related to Mechanism of Action Studies (Continued)

Reference	Cell Type	Electric Field	Results
Diniz et al., 2002	Osteoblasts (MC3T3-E1 cells)	PEMF, 15 Hz pulse burst, 7mT peak	Proliferation phase: Accelerate proliferation until confluence Enhance differentiation Increase mineralization Differentiation stage: Enhance differentiation Increase mineralization Mineralization phase: decrease bone-like tissue (related to enhancement of differentiation, not Increase number)
Spadaro and Bergstrom, 2002	Rat calvarial cells	PEMF	Parathyroid hormone-refractory effects Rapid effect on increasing Ca uptake in bone, decrease osteoclast resorption effects
Guerkov et al., 2001	Human hypertrophic and atrophic nonunion cells	4.5ms bursts of 20 pulses repeating at 15 Hz, 8 hr/day for 1, 2, or 4 days EBI	Time –dependent increase in $TGF_{\beta}1$ on Day 2 and Day 4 of atrophic No increase in cell proliferation, thymidine incorporation, ALP, collagen, PGE_2, osteocalcin
Lohmann et al., 2000	Confluent MG63 human osteoblast-like cells (from osteosarcoma)	15 HZ (EBI devices) 8 hr/day for 4 d	Decrease in proliferation Enhanced differentiation Stimulate $TGF_{\beta}1$
Hartig et al., 2000	Osteoblast-like primary cells (bovine origin)	Capacitively coupled saw-tooth pulses of 100 V and 16 Hz frequency (6kV/m across membrane)	Subconfluent: increase cell numbers Increase ALP activity Confluent cultures: stimulate matrix maturation
Bodamyali et al., 1998	Rat osteoblasts	PEMFs EBI bone healing system greater increase in cells exposed for 30 min	Increase bone nodule number and size; Increase in mRNA for bone morphogenic proteins exposure equivalent to 1 day
Brighton et al., 1992	Rat calvarial cells	60 kHz capacitively coupled field strengths of 0.0001 – 20mV/cm burst patterns continuous to 5 msec ON/495msec off 6 hours	Field strength involved in determining proliferative response 0.1, 1, and 20mV/cm continuously for 6 hours or 20mV/cm pulsed 6 hr: Increase proliferation 0.1m/cm cont and 0.0001 mV/cm pulsed: Increased differentiation

Table 1. Examples of Preclinical Articles Related to Mechanism of Action Studies (Continued)

Reference	Cell Type	Electric Field	Results
Fitzsimmons et al., 1992	Human osteosarcoma cell line (TE-85)	Model: capacitively coupled 10^{-7}, 10 – 16 Hz	14 Hz optimum Increase cell proliferation Increase in IGF-II levels Increase IGF-II mRNA
Goodman et al., 1983	Salivary gland cells *Sciara coprophila*	Biosteogen system 204 (EBI) PEMFs 5 – 90 minutes Single pulse: pulse amplitude 1.5mV/cm Pulse train 200μsec pulse duration,	Induce cell transcription
Hinsenkamp et al., 1978	Adult Frog red blood cells	(EBI) Active amplitude 4 -5 mV/cm for 0.35 sec repeated at	Chromatin modifications – induction of transcription

Animal Studies

Various animal models have been used since the early years of device development and proposed clinical use and continue to be used in the evaluation of new signals and the bone repair process. Reports of preclinical effectiveness studies in animal models were reviewed and examples are described in Tables 2 and 3. This is not intended to be an exhaustive review of this literature base. Again, both positive effects were observed in terms of bone growth/repair and improved strength (Table 2), as well as negative effects, as in no improvement in these characteristics being observed as a result of stimulation (Table 3). This does not immediately categorize such studies into the realm of "unfavorable". Dose/Response studies were conducted to try new waveforms or determine which part of a waveform may be most effective (Bassett et al., 1982; Brighton et al., 1983; and, Brighton et al., 1985; and, Matsunaga et al., 1996). It would be reasonable to conduct such studies to determine which would have the most potential clinically. Signals which are not effective in the preclinical animal testing would not be expected to proceed to clinical use. Indeed, these studies do not represent unfavorable information, but demonstrate the value of preclinical animal testing as outlined in the guidance and describe early efforts to decipher and characterize parameters which might have the best clinical potential. Animal studies indicate faster recovery of strength and load bearing capability, increases in synthesis of extracellular matrix, and formation of bridging bone, and more advanced healing (Bassett et al., 1982; Brighton et al., 1985; Guizzardi et al., 1994; Darendeliler et al., 1996; Fredericks et al., 2000; Inoue et al., 2002.) Any connection of the work reported by Fredericks and coworkers, in which the signals employed showed the positive result in animals and yet there has been a purported negative effect clinically (See K&S comments discussed in the #1 point response) does not appear to be reported in the public literature. Abundant literature exists describing potential animal models for use in testing device output parameters and their effects in the stimulation of bone growth and repair. The following table reports on effective signals.

Table 2. Studies In Which Signals Exhibit Effect

Reference	Animal Model	Signal	Results
Bassett et al., 1982	Rat – radial osteotomy	PEMF (EBI) 20 or more pulses, 200-250μsec, burst width ranging from 5 – 50ms	Significant increase in load values with 5 msec burst width, 250 μsec wide, square pulse, 5 Hz.
Brighton et al., 1983	Rabbit – tibial growth plate	Capacitively coupled, 60KHz at various voltages (2.5, 5, 10, 20 V peak to peak) (AME)	Accelerated growth in stimulated rabbits, D/R effect with 5 V peak to peak exhibiting maximum growth significant in the 5 and 10 V groups.
Brighton et al., 1985	Rabbit – fibula midshaft transverse osteotomies	Capacitively coupled	D/R curve 220mV, 250μA group and the 60KHz (0.33V/cm internal electric field) most effective. (Radiographically, stiffness, histology)
Nerubay et al., 1986	Pigs – spinal fusion	Direct current Osteostim TM S11	Radiographs and Histology – Significant increase in osteoblastic activity with bone formation
Kold et al., 1987	Horse – graft incorporation	PEMF 3 hr/ day asymmetric pulse burst of 30 ms duration at 15 Hz with each pulse of 250 μsec positive for 24mv peak and 14 μsec negative of –130mv peak (EBI)	PEMF – lower porosity Significant trend to increase in graft incorporation
Iannacone et al., 1988	Rat costochondral junction in vitro	PEMF (200 ms wide bursts repeated at 4.3Kz. Each burst of 20 pulses was 5ms wide, repeated at 15Hz Effective range 05 – 1.15mV/cm and 6.11mV/cm)	Macrophotographically – stimulates growth. Thermal effects observed.
Aaron et al., 1989	Decalcified bone matrix – from Tibial and femoral bones from rats	PEMF – 4.5 ms pulse burst duration at 15 Hz rate, each burst of20 pulses is 200 μs duration	Stimulate the synthesis of cartilage
Guizzardi et al., 1990	Rats – posterolateral arthrodeses lumbar spine (no hardware)	PEMF	4 weeks early evidence of bony fusion callus 8 weeks – fusion callus predominantly cartilaginous, calcification detectable inside
Wilmot et al., 1993	Rats – condyle growth	PEMF magnetic PEMF electrical Control Exposed 3, 7, & 14 days, 8 hr/day	Both PEMF fields had significant effect on articular zone. PEMF-M reduction in articular zone (negative chondrogenic effect)

Table 2. Studies In Which Signals Exhibit Effect (Continued)

Reference	Animal Model	Signal	Results
Guizzardi et al., 1994	Rats – posterolateral	PEMF – 18 hr/day	Acceleration of bony callus formation predominantly at early stages (4 weeks - cartilage & bone formation) Stimulation slows over time.
Matsunaga et al., 1996	Rabbits	PEMF -Varied magnetic field intensity, frequencies, & pulse durations	Significant ALP activity and osteogenesis at 0.4, 1, 2G, 25 and 50 µsec pulse durations.
Yonemori et al., 1996	Rabbit bone marrow	PEMF – 2 G, 10 Hz, pulse 25 µsec wide with /without trauma compared to DC	Intramedullary bone formation ALP activity AgNOR staining Increased most with DC then by PEMF with trauma. Need presence of reactive cells.
Darendeliler et al., 1997	Guinea pigs - mandible	PEMF Static magnetic field Control 8 hr/day	PEMF and SMF bone healing more advanced
Glazer et al., 1997	Rabbits – spinal fusion	PEMF, Orthofix	Fusion mass: Radiographs and palpation – trend towards increased fusion rate NS Tensile testing – stiffness of fusion mass SD increase Histology - Bony in growth
Grace et al., 1998	Rat –patellofemoral groove	PEMF 380 µsec, square wave 2 hr /day	1, 2, 4, 8 weeks Macroscopic evaluation Histology Microangiography PEMF accelerated early stimulation of cell proliferation, angiogenesis
Fredericks et al., 2000	Rabbit – tibial osteotomy	Low frequency, low amplitude PEMF 0.5 or 1 hr /day, with external fixation (Bursts repeated at 1.5 Hz, high frequency [>20KH] filtered from the signal, magnetic field 15 times smaller) (EBI)	Torsional testing – earlier appearance of stronger bridging bone Radiographs – accelerated formation and maturation of fracture callus Histology – Relative amount of bone to cartilage increased. (1 hr exposure better)

Table 2. Studies In Which Signals Exhibit Effect (Continued)

Reference	Animal Model	Signal	Results
Fini et al., 2002	Rabbit with Hydroxyapatite implants	PEMFs 75 Hz, 1.6mT for 3 weeks	Histomorphometric analysis – no significant changes Microhardness -- PEMF significantly higher. Bone-implant interface not significantly different compared to normal bone, but significantly higher than controls. Accelerates HA integration into trabecular bone.
Inoue et al., 2002	Canine mid-tibia Osteotomy gap (delayed union) model	PEMF (EBI) 1 hr/day from 4 weeks post surgery to 8 weeks out.	Faster recovery of load bearing, significant increase in new bone formation, higher mechanical strength, earlier and was greater Radiographic – Earlier increase in periosteal callus

Ineffective outputs have been demonstrated as shown in Table 3. This can be the result of ineffective device outputs, but also due to problems in the execution of the study. No significant differences between treated and control animals was observed by Armstrong and Brighton (1986), yet this may not have been due entirely to the device output. A failure of the animals to thrive and movement of the electrodes under test conditions may have contributed. The particular signal tested has proceeded to clinical use. Similar problems developed in experiments by Muhsin (1991). The contribution to the lack of effect by poor nutrition and movement of the animal from the treatment field cannot be ruled out. Problems with the creation of nonunions by his method were also an issue. The protocols suggested in the reports by Kahanovitz and Leisner suggest were not effective, but variations of the fields or times of exposure may have been beneficial. Such reports are not unfavorable to reclassification; they only indicate that ineffective signals can be identified in animal trials and they emphasize the need for the careful choice of animal models employed and the careful execution of the mechanics of the study and care of the animals.

Table 3. Studies in Which Signals Did Not Exhibit Effect

Reference	Animal Model	Signal	Results
Armstrong and Brighton, 1986	Rabbits – tibial growth plate	Capacitive coupling (continuous, 5V peak to peak, 60KHz sine wave) 6 weeks	NSD in tibial lengths Failure to thrive in animals contributed, movement of the electrodes
Muhsin et al., 1991	Rat tibia nonunion	PEMF for 2 – 8 weeks, Signal not specified	NSD with PEMF (problems of poor nutrition, displaced nails, movement from field tissue necrosis
Kahanovitz et al., 1994	Dogs – posterior spinal fusion	PEMF (1.5 Hz, 30msec pulse burst, 260 μsec, 1 gauss) for 0.5 or 1 hr/day	No statistical difference- radiographically, histologically

Table 3. Studies in Which Signals Did Not Exhibit Effect (Continued)

Reference	Animal Model	Signal	Results
Leisner et al., 2002	Rats – fresh ulnar fractures	PEMF (PAP IMI, Biopulse) 1μs duration, 15Hz (150-300 times greater output) twice weekly 7 weeks for 5 min.	Delayed callus formation and increased fibrous bone formation

Clinical Findings

Ten articles were identified from these additional efforts. Two articles (Articles #44, Cakirgil et al. 1989 and #140, Satter-Syed et al.1999) were part of the original search bibliography with 165 articles (see Attachment I). Of the remaining eight articles, four represent additional clinical trials or experience, although not all are related to the indications included in this reclassification effort. The remaining 4 are "review articles," meaning that they did not present original research but a review of existing research. These are directed at the treatment of nonunions and electrical stimulation in general.

Highlights from the six original research clinical articles are tabulated below, and both the original research articles and review articles are summarized below the table.

Table 4. Overview of Clinical Articles

Reference	Number of Subjects/Control	Number & Location of Nonunions	Treatment	Definition of Success	Overall Success
Cakirgil et al., 1989	21/ Compared 2 different outputs	21 pseudarthrosis: 17 from trauma 3 iatrogenic 1 congenital	PEMF	Radiographic	90%
Satter-Syed et al., 1999	19 (13 completed)/ Patient as own	19 Long bones	PEMF	Radiographic Clinical immobility, absence of pain, ability to lift leg	84.6%
*Wahlstrom, 1984	32 Total (30 completed): 15 PEMF 15 Control	32 Radius	EMF of ELF	Scintimetric examination Time to normal activity	Accelerate early healing phase
*Dunn and Rush, 1984	52 Total: 35 PEMF 17 DC	37 long bones, carpal navicular, thumb long bones	PEMF DC	Radiographs	PEMF 81% DC 82%
*Barker et al., 1984	17 (16 completed): 9 PEMF 7 dummy unit	17 Tibia	PEMF	Radiographs Clinical Exam	PEMF 77% (7/9) Sham 86% (6/7)

* Randomized controlled studies

Table 4. Overview of Clinical Articles (Continued)

Reference	Number of Subjects/Control	Number & Location of Nonunions	Treatment	Definition of Success	Overall Success
*Mammi et al., 1993	40 Total: 20 PEMF 20 dummy unit	40 Tibia	PEMF	Radiographs (blind assessment – bridging > 50% or complete union of site)	PEMF 72.2% (13/18) Control 26.3% (5/19)

* Randomized controlled studies

An additional 133 subjects are described in these studies, including treatments for long bone and other nonunions (Satter-Syed et al., 1999; Barker et al., 1984; and, Dunn and Rush, 1984), pseudarthroses of various origins (Cakirgil et al., 1989), fresh fractures (Wahlstrom, 1984) and tibial osteotomy for degenerative knee arthrosis (Mammi et al., 1993). In the first 2 studies, patients serve as their own control, due to the prior period of disability. This is not uncommon for these trials, as observed in reports previously presented. Four of the studies are randomized controlled studies as indicated in the table. Two of these studies are actually related to the indications being proposed for reclassification (Barker et al., 1984 and Dunn and Rush, 1984). None of the studies represent large populations, but are similar to those reports presented in the original petition. The variety of sites and types of nonunions and fractures are similar, as well as the descriptions of definitions of success. Effectiveness is based upon radiographic and clinical evaluation, although details presented in the reports vary with regard to these assessments. Overall, the success rates for achieving union are similar to those reported and discussed in the original petition. The rates of successful union range from 72.2% to 90% in these reports. PEMF was also shown to be similar in effectiveness to direct current stimulators in the randomized controlled study above.

In the two studies in which electrical stimulation was employed for treatment of other indications – Colles fracture (Wahlstrom, 1984) and degenerative knee arthrosis (Mammi et al., 1993) – positive effects are observed. Wahlstrom evaluated electromagnetic fields of extremely low frequency and noted acceleration in the early healing phase of fresh fractures. When PEMF was used in the treatment of degenerative knee arthrosis with tibial osteotomies, a statistically significant effect was observed in the PEMF-treated group. A higher percentage of patients in the treated group had scores of 3 or 4 in the radiographic assessment, indicating an enhanced rate of union.

The only article which **might be construed** as unfavorable is the study of tibial nonunions in which PEMF treatment did not exhibit enhanced unions as compared to controls (Barker et al., 1984). This report is widely referenced as evidence of the possible ineffectiveness of PEMF. In the small population studied, the control group had a higher success rate (86% vs. 77% in PEMF). However, the PEMF-treated group also had a higher incidence of active infections, making it difficult to determine the impact. Statistical evaluation is not possible in this small sample size. The small sample size also makes it difficult to demonstrate a true treatment effect. Furthermore, as explained in RS Medical's response to point #1, a lack of safety or effectiveness in clinical trials is not in any way unfavorable to the petition unless such findings directly relate to an existing approved Non-invasive Bone Growth Stimulator, or to a device which performed well in all preclinical tests and then failed in properly translated human studies (signal adjusted for human use). This study is equivocal and neither the device nor the related preclinical testing was identified. The petition has stated that there is a risk of ineffective output parameters associated with the device. The output parameters in this case may have been ineffective or the population not large enough to make a clear assessment. Certainly, the larger body of publicly reported clinical experience demonstrates different results than this single report.

The remaining 3 articles are review articles related to the treatment of scaphoid nonunions (Simonian and Trumble, 1994), nonunions (Rodriguez-Merchan and Forriol, 2004), and the overall effectiveness of electrical and electromagnetic energy in stimulating bone repair. It is recognized that various techniques and combinations of techniques may be necessary or are available to treat particular nonunions. While the mechanisms by which these fields induce bone repair continue to be under investigation, electrical stimulation has been shown to be an effective tool in the treatment of nonunions.

Clinical Article Summaries

Cakirgil et al., 1989 (Type of Article: Comparing PEMF Coils)
This article reports a 90% success rate in the treatment of 21 patients with pseudarthrosis resulting from trauma (17), iatrogenic (3), and congenital (1). Seven of the patients had at least one surgery prior to this treatment protocol. The patients were divided into 2 groups and treated with either a two- or four-coiled PEMF system and followed them for 2 years. No complications were reported. Union was demonstrated radiographically, although no details on the criteria are presented. The four-coiled system promoted healing sooner (2.9 months) than the two-coiled system (3.5 months), however the sample size is small and statistical evaluation was not conducted. This report provides additional anecdotal support to the existing body of evidence in the petition that demonstrates the effectiveness of PEMF in the treatment of non-unions, but little detail is provided regarding the patient population, criteria for success, or analysis. The authors suggest that these different outputs tested vary in the effectiveness, but there is not a statistical evaluation and effectiveness was demonstrated in both groups.

Satter-Syed et al., 1999 (Type of Article: Comparing PEMF to Patient as Own Control)
This article presents results from the treatment of 19 patients with delayed union or non-union of long bones. Patients have a history of nonunion of 41.3 weeks on average. Sound functional unions as characterized by: radiographic evidence of bone bridging; clinical immobility and non-tenderness; absence of pain upon stress; and, ability to lift leg when supine were counted as success. Thirteen patients completed the study which involved an average of 14 weeks of stimulation treatment for 9 - 12 hours per day and an additional 6-week period of immobilization and limited and eventual progressive weight bearing. Five patients withdrew early due to early signs of union and diminished pain and 1 patient died from unrelated complications. Eleven of the 13 patients (6 of whom were infected) achieved successful union (84.6%), a rate which is comparable to those studies discussed in the original petition. The two patients who did not achieve union had fracture gaps of larger than 1 cm. A separate control group was not employed. The rationale for this was that the patients served as their own control since they had prior long periods of conventional treatment to which they did not respond. The dose administered in this study was 0.01 and 0.1 mTesla - 100 to 1000 times less than the 16mTesla used by Bassett (#19). This study provides additional support for the effectiveness of PEMF in the treatment of

non-unions and demonstrates that variations in the waveform of the pulse and its strength can also be successful.

<u>Wahlström et al., 1984</u> (Type of Article: RCT Comparing EMF and Control)
This article presents the findings of a randomized controlled trial conducted in 32 women between the ages of 52 to 69 years with an extra-articular Colles' fracture of the radius (Colles' fractures are very common in women of this age range, frequently occurring after minor trauma). The purpose of this study was: 1) to determine whether or not electromagnetic fields of extremely low frequency (EMF of ELF) have an affect on fracture healing and 2) how electromagnetic fields affect the accumulation of ^{99m}Technetium-methylendiphosphonate (Tc-MDP) in fresh fractures. Tc-MDP values were measured by examining a series of 4 scintigrams taken at one, two, four and eight weeks after injury. Scinimetric examination was chosen because it provides a quantitative description of the activity in the fracture area. Of the 32 women enrolled into the study, 30 were evaluated (two were excluded because of faulty cables), with 15 women randomized to the control group and 15 women randomized to the treatment group. Further subdivisions were implemented for each group on the basis of the presence or absence of displacement. The device used for the treatment group consisted of a portable, battery-operated current generated and a coil with a radius of 5.4 cm and consists of 1,500 turns of 0.25 mm copper thread. The magnetic field strength at the center of the coil measured 330 At/m, corresponding to a magnetic flux density of 4.2×10^{-4} Vs/m^2 in a vacuum. The frequency of the alternating magnetic field was 1-1,000 Hz; the magnitude was 4 gauss [RMS value]. Fractures were in traction for a few minutes, then reduced and immobilized in a plaster cast for 4 weeks. Those in the treatment group had the coil fixed outside the plaster cast at the fracture site the day after injury and wore the device for a period of 4 weeks. No related complications were reported. The original displacement and the anatomical end result after four weeks of treatment were similar in both groups. Significant differences were noted at one and two weeks ($p<0.05$, $p<0.01$), with ratios for the time at which activity starts to return to normal decreasing to normal earlier in the treated group than the control group. Wahlström et al. concludes that these results do not support the belief that bone stimulation is exclusively achieved by the application of EMF of ELF, but hypothesizes that stimulation with EMF of ELF can accelerate the early healing phase of fractures, evidenced by increased scinimetric activity in the fracture area.

<u>Dunn and Rush, 1984</u> (Type of Article: RCT Comparing DC and PEMF)
This article is a review of patients treated with one of two techniques for healing nonunions – implanted bone growth stimulators and pulsed electromagnetic fields (PEMF). The implantable bone growth stimulator is a solid-state, constant-current generator that delivers 20 μA to the fracture site. The titanium cathode is coiled equally in a space spanning the nonunion, and the generator is placed in a muscle plane with an external monitor available for verification of generator output. Seventeen patients with 17 nonunions of the tibia (7), femur (5), humerus (4), and ulna (1) were treated with implantable bone growth stimulators. The duration of use and definition of success with this device were not specified. All nonunions had concomitant iliac bone grafting at the time of implantation (14) with the exception of 3 tibial nonunions. The average age for this group was 39.4 years, and the duration of disability before implantation ranged from 5 to 47 months, an average of 15.6 months. No active infections were present, but three synovial pseudoarthroses were present, one in each of the humerus, tibia, and femur. No related complications were reported. The overall success rate for this group was 82%. Thirty-

seven nonunions in 35 patients were treated with PEMF devices (32 fractures and 3 osteotomies). The article mentions the application of 10 volts of current to the coils, but additional details of the device were deferred to an unnamed manufacturer. Bones involved in this group were tibia (20 with 1 osteotomy), femur (8 with 2 osteotomies), humerus (3), carpal navicular (3), ulna (1), metacarpal (1), and proximal phalanx of the thumb (1). Bone gaps of more than 1 cm were present in one femur and one tibia. The average age for this group was 33.2 years, and the duration of disability before implantation ranged from 1 to 33 months, an average of 13.3 months. Thirty-five patients had previous operations, ranging from zero to five procedures per patient. Six had actively draining infections, and 3 others had been previously infected. Patients were required to wear the device for 10 hours/day for an average of 6.1 months. Patients wore the stimulator until there was an increase in radiographic density in the tissue of the gap and there was a patchy loss of density in sclerotic bone. Fractures that did not unite after 12 months of treatment were considered failures. Two of the failures (tibia), initially treated without bone grafts, went on to heal when combined with bone grafting and continued PEMF. No complications were reported. The overall success rate for this group was 81%, similar to many of the results reported in the original petition. Dunn and Rush demonstrated that, in addition to PEMF serving as a safe and effective method for treating nonunions, PEMF has a positive effect on actively infected nonunions, decreasing the quantity of drainage at the site of infection in five of the six actively infected nonunions. Dunn and Rush also demonstrated that, when PEMF alone was unsuccessful, combining the treatment with surgery (grafts) had an extremely high success rate.

Barker et al., 1984 (Type of Article: RCT Comparing PEMF to Control)
Barker et al. provided interim data on their double-blind study of 17 patients with tibial fractures treated with pulsed magnetic fields. Sixteen patients were evaluated; one of the patients dropped out for personal reasons. Patients were randomized to either an active or control group and were enrolled for a total of 48 weeks. The active unit produced a 1.5 mT peak, 5 msec burst waveform repeated at 15 Hz (details of the device's configuration and output are referenced in another article written by Barker), and the dummy units had an internal connection diverting their output to an internal load. Patients were recommended to use their device 12-16 hours/day (minimum session length of 1 hour) and wore the device for 24 weeks; average use in the control group was 13.8 hours/day and 13.4 hours/day for the active group. Full clinical examinations were conducted at 0, 12, 24, 36, and 48 weeks. The clinical definition of union was reported as a lack of mobility at the fracture site during mechanical stressing and a lack of movement on stress radiographs (radiographic results not reported in this article). Any fractures that failed to heal after 24 weeks were treated for an additional 24 weeks. After the first 24 weeks of treatment, 5 of the 9 active subjects had clinically united fractures compared with 5 of the 7 controls. Patients enrolled with active sepsis (3 active, 2 control) had achieved union by 24 weeks. Pain and tenderness scores tended to decrease over the first 24 weeks with no significant difference between groups at 48 weeks. At 48 weeks, 7 of the 9 active subjects progressed to union compared to 6 of the 7 controls. No related complications were noted. Potential reasons for the control groups' success ranged from a placebo effect to a high efficacy of long-term immobilization of the limb and avoidance of weightbearing. It should be noted that Barker et al. report on a small sample size, making it difficult to demonstrate a true treatment effect, but the authors state that, if it exists, is unlikely to exceed 33%, as shown by a 95% confidence interval.

The authors conclude by questioning the benefit pulsed magnetic field therapy over conservative management of nonunions.

Mammi et al., 1993 (Type of Article: RCT Comparing PEMF with Control)
This study reports on the effect of pulsed electromagnetic field stimulation on 40 patients who were treated with valgus tibial osteotomy for degenerative arthrosis of the knee. Patients were randomized to either a control group (dummy unit) or active group (20 patients per treatment arm), with an average age of 61 years for the control group and 62 years for the active group. All patients were operated on by the same author of this article and followed the same post-operative treatment regimen. Patients wore non-weightbearing casts for the first 30 days and a shorter weightbearing cast for the next 30 days. Stimulation, regardless of treatment group, was initiated 3 days post-procedure, and patients were to use the device for 8 hours/day and duration of 60 days, with an average reported use of 7.3 +/- 3.3 SD hours for the control group and 7.0 (2.6, SD) for the active group. The pulse generator used for the active group was an IGEA stimulator, creating single voltage pulses at a frequency of 75 Hz, each lasting 1.3 milliseconds, with an induced electric field measuring 3.0 +/- 0.5 mV. Radiographs were used to analyze the patients' progress, with films taken one day after the operation, and at Days 30, 60 and 180 post-operatively. Starting at post-operative Day 60, radiographs were independently rated on a scale of 1 to 4 (score of 1 = osteotomy line is still clearly evident; score of 2 = osteotomy seen of 50% of its length with some signs of bridging; score of 3 = osteotomy site still visible, but bridging of more than 50% of the osteotomy; score of 4 = complete union of the osteotomy site, with bridging seen over all lengths in the AP and lateral) by four, blinded orthopedic surgeons (the authors note that Day 30 was too difficult to score, due to the presence of the plaster casts). Results were reported on 19 control group patients and 18 active group patients (one patient in each group withdrew consent, and one patient in the active group was found to be ineligible). In the control group, 14 of the 19 patients (73.7%) scored in either the first or second category compared to 5 of 18 active group patients (27.8%). Five of the 19 control group patients (26.3%) versus 13 of the 18 active group patients (72.2%) scored in either the third or fourth category ($p<0.006$), making these observations statistically significant. Average scores for the control group were 2.1 and 3.0 for the active group. No related complications were noted. This study supports the enhanced rate of union that is generated by PEMF devices for the treatment of osteotomies.

Review Article Summaries

Aaron, Ciombor, and Simon, 2004 (Type of Article: Review of DC, CC, and IC)
This review article discusses the in vitro, in vivo, and clinical efficacy of electric and electromagnetic energy in stimulating bone repair. The techniques for stimulating bone with electric and electromagnetic fields, either by direct electrical current (DC) or noninvasively by capacitive coupling (CC) or inductive coupling (IC) are reviewed. DC techniques stimulate osteogenesis at the cathode at currents of 5 to 100 μA. When applying potentials of 1 to 10 V at frequencies of 20 to 200kHz, capacitive coupling can generate electric fields in the tissue of approximately 1 to 100 mV/cm. Depending on the waveform configuration, time varying magnetic fields of 0.1 to 20 G can also be generated in bone by IC with an external time varying or pulsed electromagnetic field (PEMF), producing a voltage-gradient of 1 to 100 mV/cm. The application of these fields (DC, CC, and IC) in skeletal cell and organ cultures has positively

demonstrated osteogenesis in models such as rat calvarium, osteoblasts, and osteoprogenitor cells. Overall, the studies cited in this article show that cells involved in endochondral bone formation can be stimulated at several phases of their cell cycle when stimulated by an appropriately configured electric and electromagnetic field. The effects of electric and electromagnetic fields and their ability to stimulate osteogenesis in animal models, such as the rabbit fibula osteotomy, rabbit fibula delayed union, and dog tibia osteotomy, are also reviewed. Capacitively coupled fields have been reported to improve the mechanical strength of experimental fractures and healing osteotomies, also increasing the stiffness of treated osteotomies when treated with a field of 60kHz, 200 mV, and 20 μA. In a dosimetry study conducted by Fredericks et al. 2000, osteotomies treated with PEMF for 60 minutes/day reached intact torsional strength in 14 days after osteotomy in comparison to 21 days for osteotomies treated 30 minutes/day for 28 days in the sham-treatment group. The article then discusses the reported successes of DC, CC, and IC in enhancing bone formation and improving spinal fusion success rates. Kahanovitz et al. 1984 conducted radiographic and histologic studies using IC stimulation to show an earlier incorporation of bone graft, improved bone formation, and a more organized fusion mass. The authors conclude the in vivo section of the article with a demonstrated correlation between the IC PEMF field producing a temporal acceleration and quantitative increase in endochondral bone formation. In a study by Ciombor et al. 2002, exposure to an IC PEMF resulted in the increase of proteoglycan and collagen, leading to an increase in chondrogenesis. The extracellular matrix synthesis showed corresponding increases in mRNA transcripts for proteoglycan and collagen, and a larger fraction of the proteoglycan was specific for cartilage. A clinical discussion on the effectiveness of electric and electromagnetic fields for the treatment of various conditions follows (e.g. fractures and osteotomies, anterior and posterior spine fusions, augmentation of bone grafts). The authors state that the efficacy of DC, CC, and IC on delayed and nonunions of long bone fractures is largely based on observational studies and smaller controlled studies, justifying that, those studies reporting the small numbers of patients who went on to heal spontaneously, demonstrated self-controlled or internally-controlled populations. Those studies employing actual controls reported efficacies equivalent to bone grafting. While the authors acknowledge heterogeneity in study designs, overall, the studies demonstrate that exposure to electric and electromagnetic techniques stimulates bone repair.

<u>Kahanovitz, 2002</u> (Type of Article: Scientific and Clinical Review of Electrical Stimulation)

This article discusses the variation in scientific and clinical effectiveness observed with electrical stimulation devices (e.g. direct current electrical stimulation (DCES), pulsed electromagnetic fields (PEMF), combined magnetic fields (CMF), capacitive coupling) when used as an adjunct to increase the success of lumbar spinal fusion. Overall, the author recognizes these devices as valid adjuncts for achieving solid lumbar spinal fusions. The configuration, proper device placement, and the general instructions for use of the DCES, PEMF, CMF, and capacitive coupling devices are reviewed, followed by overviews of the possible mechanisms of action. With respect to PEMF devices, hypotheses range from alterations in cell membrane potentials to increases in calcium influx into bone cells. A study by Aaron et al. demonstrated that PEMF was able to enhance the synthesis of cartilage molecules and subsequent endochondral calcification, and was also able to mimic the bone healing process by showing increased calcification in a rat model. PEMF may have an effect on the differentiation and proliferation of target cells, also stimulating matrix and growth factor production. Other studies, such as those conducted by Bodamyali et al. and Sahinoglu et al. showed that, when compared to controls, PEMF was found to increase level of bone morphogenic protein (BMP)-2 and BMP-4 in rat calvarial osteoblasts, with effects being directly correlated to the duration of PEMF exposure. While the true mechanism of action may not be completely understood for capacitive coupling devices, studies by Lorich et al. and Zhuang et al. were able to demonstrate the biochemical pathway that elicits an osteogenic response. By observing cellular proliferation between electrically stimulated and control groups, a signal transduction pathway was found to involve transmembrane calcium translocation or movement through voltage-gated calcium channels, resulting in increases in prostaglandin E2 and activation of calmodulin. The inositol phosphate pathway, found to be dominant in mechanically stimulated bone cells, was noted to be dormant in electrically stimulated bone cells. The author recognizes that, in addition to the physiological and biomechanical differences in healing between patients, there are clinical differences in success between the different types of electrical stimulation devices. The majority of data shows that capacitive coupling is superior to PEMF (the author reports that, at the time of the article's publication, the only trial on CMF had just been presented at a conference), but not as statistically significant as DCES as an adjunct to posterior spinal fusion.

<u>Rodriguez-Merchan and Forriol, 2004</u> (Type of Article: Review of Treatment of Nonunions)

This review article discusses what data are known about nonunions and the various methods that can be applied to treat nonunions. While the authors state that it is difficult to provide a universally accepted definition of nonunion, generally, nonunions are comprised of fractures that fail to heal over a 6 to 8 month period. Mechanical factors known to impact the healing of a nonunion are excess motion, a large interfragmentary gap, and loss of blood supply. Excess motion is attributed to inadequate immobilization at the fracture site by internal or external devices. Infection is cited to predispose patients to nonunions, due to the factors such as the loosening of implants or the creation of gaps caused by osteolytic infectious granulation tissue. Smoking is recognized as a factor that can result in complications, such as delayed consolidation and a high incidence of nonunion. The pathophysiology of nonunions is discussed, stating that fracture healing can be affected by factors, such as collagenase production by macrophages and fibroblasts that reside in the fracture gap or an overall absence of peripheral nerves in the nonunion tissue, which could impact the monitoring of bone strain by proprioceptors. Aside from healing a nonunion, additional objectives for proper treatment of nonunions are identified and include: correcting unacceptable shortening, angulation, rotation at the time of operative internal fixation, removing any infection present at the fracture site, and to obtain a functional limb. The various methods that can be employed to achieve the aforementioned objectives are discussed, ranging from internal treatment methods (e.g. screw fixation, plate fixation, intramedullary nailing), external treatment methods, a combination of internal and external fixation, and bone grafting. The article goes on to discuss biophysical enhancement, one such method being electrical stimulation. The authors state that electrical stimulation have been demonstrated to be effective in treating hypertrophic nonunions (these types of nonunions show decreased vascularity and callus formation, with radiographs depicting a horseshoe or elephant-foot configuration), and to be less effective in treating atrophic nonunions (these types of nonunions show little callus formation around a fibrous-filled fracture gap) and in the presence of a gap. The authors state that electrical stimulation can best be used to treat diaphyseal hypertrophic nonunions, with little or no deformity, gap, or shortening. Other methods of biophysical enhancement that are discussed by the authors are ultrasound stimulation, high-energy extracorporeal shock waves, autogenous bone marrow injected percutaneously, and osteoinductive molecules. The experimental models of nonunion and pseudarthrosis are also reviewed. While an experimental model has not been universally established, rodents and dogs are frequently used as models to demonstrate the skeletal repair process. The authors discuss results of several studies examining the interactions between the immune, hematopoietic, and musculoskeletal systems. Cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), are recognized as having a potential role in the skeletal repair process. In a study conducted by Lawson et al., the expression of collagenase Type III was found in nonunions, characterized during the initial phases of osteoblastic differentiation and not observed in normal osteoblasts. An important process in consolidation of bone is the reinnervation of the periosteum, and nerve growth factor was noted to be expressed in the fracture callus, demonstrating the involvement of nerves in the bone repair process. This review article recognizes that, while additional research to treat a particular nonunion is required, a great deal of knowledge has been obtained regarding the general principles of nonunions.

Simonian and Trumble, 1994 (Type of Article: Review of Scaphoid Nonunions)
This article discusses the history and treatment of scaphoid nonunions, the incidence of such fractures only second to those of the distal radius. The various methods for classifying scaphoid fractures are reviewed, followed by those methods to use for early diagnosis (e.g. radiographs taken at 10 to 14 days to confirm the presence of a fracture or a bone scan taken 24 hours after injury). Avascular necrosis of the proximal pole of the scaphoid is used as a predictive factor in the success of surgeries to correct scaphoid nonunions, and the use of magnetic resonance (MR) imaging to measure such factors are explained. The current nonoperative treatments were reviewed, beginning with no treatment, then progressing to cast immobilization and electrical stimulation. Within this article, the use and effectiveness electrical stimulation is regarded as 'highly controversial,' but states that 'the results are satisfactory enough to justify its consideration as an alternative treatment.' With many reports on the degenerative changes of scaphoid nonunions and the link with osteoarthritis, many operative techniques are used to manage these nonunions. The various techniques, ranging from bone grafting, internal fixation, and salvage procedures, are discussed, concluding with the preferred methods of treatment employed by Simonian and Trumble.